PCT/DK03/00220

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

Rec'd PCT/PTO 04 OCT 2004

10/509911

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

THALSØ-MADSEN, Birgit
Head of Patent Section
Leo Pharma A/S
Industriparken 55
DK-2750 Ballerup
DANEMARK

Kopi til TOD — skal vi anmode om at få rettet fejlen, der er forekommet?

Date of mailing *(day/month/year)* 23 October 2003 (23.10.03)	
Applicant's or agent's file reference 618	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK03/00220	04 April 2003 (04.04.03)	05 April 2002 (05.04.02)

Applicant

LEO PHARMA A/S

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   AU, AZ, BY, CH, CN, CO, DE, DZ, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-*bis*)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 23 October 2003 (23.10.03) under No. 03/087121

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph, be 30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For filing a **demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's **sole responsibility** to monitor all these time limits.

HVI ER INTERESSERET I POSITION
SE 065 609 SOM ER OPGIVET?

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.(41-22) 740.14.35	Authorized officer Judith Zahra Telephone No.(41-22) 338.91.11

Form PCT/IB/308 (April 2002)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 618	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00220	International filing date *(day/month/year)* 04.04.2003	Priority date *(day/month/year)* 05.04.2002
International Patent Classification (IPC) or both national classification and IPC C07J41/00		
Applicant LEO PHARMA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.10.2003	29.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Friebel, F Telephone No. +49 89 2399-8552

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00220

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-35 as originally filed

Claims, Numbers

1-36 filed with telefax on 14.04.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 33-36

because:

☒ the said international application, or the said claims Nos. 33-36 - IA relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-24 - in part

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations

see separate sheet

point III:

The subject-matter of Claims 1 to 24 has been only searched in part; the search is restricted to those parts which relate to compounds according to Claims 25 and 26 (see the comment adjacent to the Intern.Search Report).

Claims 33-36 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

point V:

The present application claims steroid derivatives containing up to 3 polyamine radicals; said compounds exhibit an antimicrobal activity.

Relevant prior art are the following documents:

D1: **PINHAS H.et al.**: '6-amino derivatives of stigmastanol and cholestanol.' JOURNAL OF MEDICINAL CHEMISTRY. 1971, vol. 14, no. 11, November 1971 (1971-11), pages 1048-1049; see the compounds 5-7 and 10-12

D2: **US-A-3 013 008** (COUNSELL RAYMOND E) 12 December 1961 (1961-12-12); see the compounds of Claims 4,5 and 8-10

D3: **BELLINI, A. et al.**: 'Antimicrobial activity of cholane compounds' EUR. J. MED. CHEM. vol. 18, no. 2, 1983, pages 185-190; see the compounds V, XII, XIX, XXVI

To delimit the presently scope of claims from these prior art compounds the Applicant has added a disclaimers at the end of Claim 1; Novelty is acknowledged (Art.33(2) PCT). For the sake of completeness the Applicant is already now informed that the admissibility of the disclaimer with regard to the 3rd reference will be decided in the reg.phase before the EPO (➡no accidental disclosure).

As concerns the pharm.activity neither D1 nor D2 refers to an antibiotic activity. However, D3 explicitly underlines the antimicrobial activity of such compounds; this reference is therefore relevant under Art.33(3) PCT.

The same applies to the document

D4: **WO 00 09137** A (RAO MEENA ;KINNEY WILLIAM (US); MAGAININ PHARMA (US); NOECKER LINC) 24 February 2000 (2000-02-24)

which is also highly relevant under Art.33(3) PCT.

The line of argumentation presented by the Applicant in order to overcome the obviousness objections is not persuasive; the Art.33(3) objection is maintained.

As concerns **D3** the following is to be noted:
The argument based on graphs 1 to 4 saying that the person skilled in the art would not take D3 into consideration in order to solve the problem addressed in the instant case is misleading. On the contrary, the cholane derivatives with the branched polyamine chain show indeed a high activity and therefore clearly constitute an incentive for the art skilled person to further elaborate this concept.

As concerns **D4** the Applicant in particular relies on the *'branched amine feature'* which according to his point of view is essential to the instantly claimed subject-matter. This however is not corroborated by the language of the claims presently on file. The proviso on page 1 of Claim 1 makes compulsory (as a minimal requirement) that '...at least one R is different from hydrogen.' The IPEA is of the opinion that a linear polyamine chain with only one further substituent on the terminal amino group still constitutes a linear chain and not a branched chain. Let alone that the polyamine side chains of the partial formula XII and XIII (Claim 25) are only distinguished from D4 by an additional methyl group on the middle nitrogen which despite this minor modification is still deemed to be a liner polyamine chain. It is already now emphasized that in the reg. the Applicant will again be invited to file comparative date.

As concerns the document **WO 02/077007** which is an earlier Application of LEO PHARMA the IPEA assumes that the present application is entitled to the priority date claimed.

For the assessment of the present claims 33-36 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.